TERT gene

telomerase reverse transcriptase

Normal Function

The *TERT* gene provides instructions for making one component of an enzyme called telomerase. Telomerase maintains structures called telomeres, which are composed of repeated segments of DNA found at the ends of chromosomes. Telomeres protect chromosomes from abnormally sticking together or breaking down (degrading). In most cells, telomeres become progressively shorter as the cell divides. After a certain number of cell divisions, the telomeres become so short that they trigger the cell to stop dividing or to self-destruct (undergo apoptosis). Telomerase counteracts the shortening of telomeres by adding small repeated segments of DNA to the ends of chromosomes each time the cell divides.

In most types of cells, telomerase is either undetectable or active at very low levels. However, telomerase is highly active in cells that divide rapidly, such as cells that line the lungs and gastrointestinal tract, cells in bone marrow, and cells of the developing fetus. Telomerase allows these cells to divide many times without becoming damaged or undergoing apoptosis. Telomerase is also abnormally active in most cancer cells, which grow and divide without control or order.

The telomerase enzyme consists of two major components that work together. The component produced from the *TERT* gene is known as hTERT. The other component is produced from a gene called *TERC* and is known as hTR. The hTR component provides a template for creating the repeated sequence of DNA that telomerase adds to the ends of chromosomes. The hTERT component then adds the new DNA segment to chromosome ends.

Health Conditions Related to Genetic Changes

Idiopathic pulmonary fibrosis

At least 70 mutations in the *TERT* gene have been identified in people with the progressive lung disease idiopathic pulmonary fibrosis. This condition causes scar tissue (fibrosis) to build up in the lungs, which makes the lungs unable to transport oxygen into the bloodstream effectively. Mutations in the *TERT* gene have been found in cases that run in families (familial pulmonary fibrosis) and, less commonly, in isolated (sporadic) cases. Some individuals with idiopathic pulmonary fibrosis due to *TERT* gene

mutations have family members with other features of dyskeratosis congenita (described above), such as aplastic anemia or cancer.

Mutations in the *TERT* gene reduce or eliminate the function of telomerase, which allows telomeres to become abnormally short as cells divide. The shortened telomeres likely trigger cells that divide rapidly, such as cells that line the inside of the lungs, to stop dividing or to die prematurely. In people with idiopathic pulmonary fibrosis, shorter telomeres are associated with a more severe disease and a quicker decline in lung function. Additional research is needed to confirm how shortened telomeres contribute to the progressive scarring and lung damage characteristic of idiopathic pulmonary fibrosis.

Idiopathic pulmonary fibrosis is a complex disease that is probably caused by a combination of genetic and environmental factors. Studies suggest that many affected people with *TERT* gene mutations may have also been exposed to environmental risk factors, such as cigarette smoke or certain kinds of dust or fumes. It is possible that mutations in the *TERT* gene increase a person's risk of developing idiopathic pulmonary fibrosis, and then exposure to certain environmental factors can trigger the disease.

Dyskeratosis congenita

At least 40 mutations in the *TERT* gene have been identified in people with dyskeratosis congenita. This disorder is characterized by changes in skin coloring (pigmentation), white patches inside the mouth (oral leukoplakia), and abnormally formed fingernails and toenails (nail dystrophy). People with dyskeratosis congenita have an increased risk of developing several life-threatening conditions, including cancer and a progressive lung disease called pulmonary fibrosis. Many affected individuals also develop a serious condition called aplastic anemia, also known as bone marrow failure, which occurs when the bone marrow does not produce enough new blood cells.

Most of the *TERT* gene mutations that cause dyskeratosis congenita change single protein building blocks (amino acids) in the hTERT protein, causing it to be unstable or dysfunctional. The mutations interfere with telomerase function, leading to impaired maintenance of telomeres and reduced telomere length. Cells that divide rapidly are especially vulnerable to the effects of shortened telomeres. As a result, people with dyskeratosis congenita may experience a variety of problems affecting quickly dividing cells in the body such as cells of the nail beds, hair follicles, skin, lining of the mouth (oral mucosa), and bone marrow.

Breakage and instability of chromosomes resulting from inadequate telomere maintenance may lead to genetic changes that allow cells to divide in an uncontrolled way, resulting in the development of cancer in some people with dyskeratosis congenita.

Breast cancer

MedlinePlus Genetics provides information about Breast cancer

Cholangiocarcinoma

MedlinePlus Genetics provides information about Cholangiocarcinoma

Melanoma

MedlinePlus Genetics provides information about Melanoma

Cancers

Mutations in the *TERT* gene have been associated with an increased risk of various cancers, in particular a type of skin cancer called melanoma and a form of blood cancer called acute myeloid leukemia. Researchers suggest that these mutations may impair telomere maintenance and result in DNA damage. Damage to genes that help control the growth and development of cells can cause uncontrolled cell growth and lead to development of these cancers.

Other disorders

TERT gene mutations have also been found in people with isolated aplastic anemia, a form of bone marrow failure that occurs without the other physical features of dyskeratosis congenita. Researchers suggest that mutations affecting different parts of the telomerase enzyme may account for the absence of these features. Some believe that isolated aplastic anemia caused by *TERT* gene mutations may actually represent a late-onset form of dyskeratosis congenita in which physical features such as nail dystrophy are mild and may not be noticeable.

Other Names for This Gene

- EST2
- hEST2
- TCS1
- telomerase catalytic subunit
- telomerase-associated protein 2
- TERT_HUMAN
- TP2
- TRT

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of TERT (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=7015[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28TERT%5BTI%5D%29+OR+%28telomerase+reverse+transcriptase%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- APLASTIC ANEMIA (https://omim.org/entry/609135)
- TELOMERASE REVERSE TRANSCRIPTASE (https://omim.org/entry/187270)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/7015)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=TERT[gene])

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Genomic Location

The *TERT* gene is found on chromosome 5 (https://medlineplus.gov/genetics/chromosome/5/).

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